



BRAZILIAN JOURNAL
OF MEDICAL AND BIOLOGICAL RESEARCH

www.bjournal.com.br

ISSN 1414-431X
Volume 45 (10) 875-994 October 2012

BIOMEDICAL SCIENCES

Braz J Med Biol Res, October 2012, Volume 45(10) 921-928

doi: 10.1590/S0100-879X2012007500106

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The Brazilian Journal of Medical and Biological Research is partially financed by



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Effect of different durations of overdistention on rat bladder function and morphology

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Abstract

We investigated the contribution of the duration of overdistention (DOD) to rat bladder function and morphology and explored its possible molecular mechanisms. Bladder overdistention was induced in male Sprague-Dawley rats (200-250 g) by an infusion of saline. Forty rats were divided into 5 groups submitted to different DOD, i.e., 1, 2, 4, and 8 h, and control. Bladder function was evaluated by cystometry. Morphological changes were observed by light and transmission electron microscopy. Compared to control (44.567 ± 3.472 cmH₂O), the maximum detrusor pressure of groups with 2-, 4- and 8-h DOD decreased significantly (means ± SEM): 32.774 ± 3.726, 31.321 ± 2.847, and 29.238 ± 3.724 cmH₂O. With the increase of DOD, inflammatory infiltration and impairment of ultrastructure were more obvious in bladder tissue. Compared to control (1.90 ± 0.77), the apoptotic indexes of groups with 1-, 2-, 4-, and 8-h DOD increased significantly (6.47 ± 2.10, 10.66 ± 1.97, 13.91 ± 2.69, and 18.33 ± 3.28%). Compared to control (0.147 ± 0.031/0.234 ± 0.038 caspase 3/β-actin and Bax/Bcl-2 ratios), both caspase 3/β-actin and Bax/Bcl-2 ratios of 1-, 2-, 4-, and 8-h DOD increased significantly (0.292 ± 0.037/0.508 ± 0.174, 0.723 ± 0.173/1.745 ± 0.471, 1.104 ± 0.245/4.000 ± 1.048, and 1.345 ± 0.409/8.398 ± 3.332). DOD plays an important role in impairment of vesical function and structure. With DOD, pro-apoptotic factors increase and anti-apoptotic factors decrease, possibly contributing to the functional deterioration and morphological changes of the bladder.

Key words: Acute urinary retention; Bladder overdistention; Urodynamics; Ultrastructure; Apoptosis; Rat

Introduction

Acute urinary retention (AUR) is a common complication in men with benign prostatic hyperplasia and/or low urinary tract symptoms (1,2). A 2-year study of finasteride showed that approximately 3% of placebo-treated subjects suffered an episode of AUR (3). As an indication for prostatectomy, AUR accounts for 24-42% of patients undergoing prostatectomy (4).

Traditionally, AUR has been thought to simply produce stretch damage of the detrusor muscle and other bladder microstructures, resulting in reduced contractility of the detrusor muscle. Animal studies have indicated that the biochemical and metabolic status of the bladder is altered after overdistention (5,6). Ischemia-reperfusion injury after overdistention plays an important role in prolonged bladder dysfunction (7,8). Overdistention induces increased pressure in the bladder and reduction in blood flow to bladder tissue, resulting in partial ischemia and hypoxia. After

decompression, the blood supply recovers and oxygen free radicals are generated, ultimately leading to bladder dysfunction.

The structural changes of the bladder occurring with AUR time have been confirmed by Gabella and Uvelius (9). However, ischemia-reperfusion injury was not considered and bladder function was not investigated simultaneously in their study. Furthermore, few reports are available about the role of apoptosis and related factors in bladder dysfunction after AUR.

In the present study, we created a new overdistention rat model and determined the morphological and functional changes of the bladder with duration of the condition. We also observed the changes of apoptotic rates and apoptosis-related factors in bladder tissue after different durations of overdistention (DOD). We attempted to determine whether different DOD could result in different severities of blad-

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Received June 1, 2011. Accepted May 28, 2012. Available online June 29, 2012. Published September 3, 2012.

der impairment, to determine the relationship between morphological and functional changes, and to prove the important role of apoptosis and its related factors in the bladder dysfunction occurring after overdistention.

Material and Methods

Animal model

All animal care and experimental protocols were in accordance with the guidelines of NIH regarding the care and use of animals for experimental procedures, and were approved by the animal laboratory of Zhejiang University. Forty male Sprague-Dawley rats (200-250 g, 3-4 months of age) were anesthetized with urethane (1.0 g/kg, *ip*) and allocated to five groups of 8 rats each: sham-operated control, DOD for 1 h, DOD for 2 h, DOD for 4 h, and DOD for 8 h. The bladder was exposed through a lower abdominal midline incision. After emptying the bladder, we ligated the foreskin with a 3-0 silk thread. A 24-G catheter was inserted into the apex of the bladder dome and connected to an infusion pump and 0.9% saline was infused (0.1 mL/min) at 37°C up to a total volume of 1.0 mL, which was approximately twice the mean bladder volume of 0.5 mL. The status of overdistention was kept for 1, 2, 4, and 8 h, respectively. In the control group, the bladder was exposed and punctured as in other groups but without saline infusion. A cystometric study was performed after overdistention relief for 1 h.

Cystometric study

After emptying the bladder, we inserted a 24-G catheter into the apex of the bladder dome. The catheter was connected to an infusion pump and 0.9% saline was infused (0.1 mL/min) at 37°C until micturition was detected. The catheter was also connected to an external pressure transducer for the measurement of intravesical pressure. Data were recorded on a personal computer via a bridge amplifier. The following parameters were recorded: intravesical pressure at the beginning and end of filling, bladder capacity, and maximum detrusor pressure during voiding. Detrusor overactivity and detrusor acontraction are reported according to the definition of the International Continence Society (10).

Contractile responses assayed *in vitro*

After cystometry, rats were sacrificed and the bladder was removed at the level of the bilateral urethral orifices. Approximately 8-mm long and 2-mm wide detrusor strips were prepared from the bladder body and placed in an organ bath containing Krebs-Hanseleit solution (37°C, pH 7.4) continuously infused with 95% O₂ and 5% CO₂. After preparation, one end of each prepared strip was connected to a muscle holder and the other end to an FDT 10 force displacement transducer (Biopac, USA) with a silk thread. Before constructing concentration-response curves,

muscle strips were stretched to the length of optimal force development and then equilibrated for 60 min. During this period, the Krebs-Hanseleit solution was replaced every 15 min. Electrical-field stimulation (EFS) was applied to the strips at 2, 4, 8, 16, and 32 Hz for 20 s with 1-ms, 80-V pulses using an S88 stimulator (Grass Instruments, USA). Next, the maximum contractile responses to 0.3, 1.0, 3.0, 10, and 30 μm carbachol and 120 mM potassium chloride were determined. The strips were washed three times with fresh buffer between studies with different drugs. The data were recorded using the MP 100 software (Biopac).

Morphological examination

To assess inflammatory infiltrates, sections were stained with hematoxylin and eosin and examined by light microscopy. To observe the ultrastructure of the bladder tissues, sections were stained with uranyl acetate and lead citrate and then examined by transmission electron microscopy.

Terminal deoxynucleotidyl transferase-mediated nick-end labeling (TUNEL) assay

Apoptosis was detected by the TUNEL assay. Formalin-fixed, paraffin wax-embedded tissue sections were deparaffinized and stained by the TUNEL-avidin-biotin-complex method. Ten high-power (400X) fields were randomly selected in each section. We selected different numbers of fields according to the thickness of different layers: 2 in the mucosa, 2 in the submucosa, 4 in the detrusor, and 2 in the serosa. The number of positive cells and total cells was recorded and analyzed. The apoptotic index was calculated as number of positive cells/number of total cells x 100%.

Western blotting

To measure the expression of Bcl-2, Bax, and caspase-3 at the protein level, bladder samples were quickly frozen in liquid nitrogen, and stored at -70°C for protein isolation. The tissues were homogenized with a pre-chilled mortar and pestle in extraction buffer. After complete homogenization, the sample was kept at 4°C for 30 min, centrifuged at 12,000 g for 12 min, and the supernatant was collected. Subsequently, protein concentration was determined by the Bio-Rad protein assay (Bio-Rad Laboratories, USA). The antibodies used for Western blotting analysis were goat polyclonal antispectrin α antibody (Santa Cruz Biotechnology Inc., USA), mouse anti-actin monoclonal antibody, mouse anti-Bcl-2 monoclonal antibody, mouse anti-Bax monoclonal antibody, and rabbit anti-caspase-3 (CPP32) monoclonal antibody (NeoMarkers, USA).

Statistical analysis

Data are reported as means ± SEM and the differences between groups were compared by ANOVA. P < 0.05 was considered to be statistically significant.

Results

All rats survived and their data were collected, except for one rat in the group with 8-h overdistention.

Results of the cystometric study

The bladder capacity and maximum detrusor pressure decreased significantly in groups with 2-, 4-, and 8-h DOD compared to control. Bladder compliance also decreased significantly in the groups with 4- and 8-h overdistention. With the increase of DOD, more rats suffered detrusor overactivity and acontraction (Table 1).

Contractile responses assayed *in vitro*

In the groups with 2-, 4- and 8-h overdistention, the maximal contractile responses induced by 32-Hz EFS, 30 μ m carbachol, and 120 mM potassium chloride decreased significantly compared to control. The longer the AUR duration, the smaller the maximal contractile response (Figure 1).

Morphological examination

A few white blood cells (WBCs) infiltrated the mucosa and submucosa of bladder tissues in the 1- and 2-h DOD groups, while few WBCs were seen in muscles and in the external membrane. In the 4-h DOD group, acute inflammation was present in all layers of the bladder and was most obvious in the submucosa. The vessels were hyperemic and dilated, quite a few WBCs infiltrated and the inflammation of the mucosa was also obvious. Even in the muscle, we could see a few WBCs. In the 8-h DOD group, the inflammation was more extensive than in the 4-h DOD group. Hemorrhage was seen in the submucosa and some mucosal cells were sloughed (Figure 2). Although the inflammation in muscle was less than in the other layers, it was more extensive than that of the 4-h DOD group.

Ultrastructural changes of the detrusor

The ultrastructural changes of muscles and organelles

from the 1- and 2-h DOD groups were not obvious compared to the control. In the 4-h DOD group, muscle cells were still intact and lined up in an orderly manner. However, the intercellular gap began to broaden while at the same time some mitochondrial ridges disappeared and vacuoles emerged. In the 8-h DOD group, muscle cells lined up in a disorderly manner and the intercellular space was obviously wider and infiltrated with inflammatory cells. The mitochondria were heavily swollen and their ridges disappeared (Figure 3).

TUNEL assay

Using the TUNEL method, we found that different groups exhibited varying degrees of positive apoptosis staining. The apoptotic indexes increased with prolonged DOD from $6.47 \pm 2.10\%$ in the group with 1-h DOD to $18.33 \pm 3.28\%$ in the group with 8-h DOD (Figure 4).

Apoptosis-related factors

Western blotting showed that the pro-apoptotic factors Bax and caspase-3 were up-regulated, while the anti-apoptotic factor Bcl-2 was down-regulated with the increase of DOD (Figure 5).

Discussion

In the present study, we improved the overdistention rat model. Some investigators induced overdistention by clamping the distal urethra of rats with a small clip, which could hurt the urethra to some extent and affect the result of cystometry (7,11). Our model was induced by ligating the foreskin, which did not hurt the urethra and ensured correct data for the urodynamic study. According to the literature, the volume of saline infused in the bladder varies in different overdistention models. It was 3 mL in the rat model used by Saito and Miyagawa (7) and Saito et al. (11) and 1.5 mL in the model used by Hong et al. (12). So far, no standard infusion volume has been established for the overdistention model. However, many investigators have infused a saline volume twice the bladder volume to induce

Table 1. Cystometric results of rats undergoing different durations of overdistention.

Group	N	Capacity (mL)	Compliance (mL/cmH ₂ O)	Pdet (cmH ₂ O)	DO ratio	DA ratio	Non-micturition ratio
Control	8	0.479 \pm 0.104 ^{cde}	0.488 \pm 0.158 ^{de}	44.567 \pm 3.742 ^{cde}	0/8	0/8	0/8
DOD							
1-h	8	0.472 \pm 0.090 ^{cde}	0.495 \pm 0.090 ^{de}	45.098 \pm 3.649 ^{cde}	2/8	0/8	0/8
2-h	8	0.420 \pm 0.073 ^{ab}	0.336 \pm 0.061 ^{de}	32.774 \pm 3.726 ^{abe}	3/8	0/8	1/8
4-h	8	0.326 \pm 0.040 ^{ab}	0.323 \pm 0.018 ^{abc}	31.321 \pm 2.847 ^{ab}	5/8	2/8	2/8
8-h	7	0.296 \pm 0.082 ^{ab}	0.259 \pm 0.044 ^{abc}	29.238 \pm 3.724 ^{ab}	5/7	2/7	3/7

Pdet = maximum detrusor pressure during voiding; DO = detrusor overactivity; DA = detrusor acontraction. Data were analyzed by ANOVA: ^aP < 0.05 vs control group; ^bP < 0.05 vs 1-h duration of overdistention (DOD) group; ^cP < 0.05 vs 2-h DOD group; ^dP < 0.05 vs 4-h DOD group; ^eP < 0.05 vs 8-h DOD group.

the overdilatation model. By testing male Sprague-Dawley rats weighing 200-250 g repeatedly, we found that the mean bladder volume was 0.5 mL and therefore we set 1 mL as the volume for the overdilatation model.

According to the literature, the severity of bladder dysfunction varies at different times after overdilatation relief (7,12). Saito et al. (11) measured the contractile responses to carbachol before and at the beginning of overdilatation, at the time of overdilatation relief, and 30 min after catheterization. They found that the maximum contractile responses of the bladder to carbachol did not change significantly before or at the beginning of overdilatation and at the time of overdilatation relief. However, the maximum contractile response decreased significantly at 30 min after catheterization. In order to take the ischemia-reperfusion injury into account, we performed the cystometric tests 1 h after overdilatation relief, while the bladder tissues for the

assay of the contractile responses and for pathologic and molecular biology tests were collected immediately after the cystometric tests.

The function of the urinary bladder is to collect and store urine at low intravesical pressures, and then to periodically expel the urine by a coordinated sustained contraction. When AUR occurs, the intravesical pressure is elevated, causing ischemia and anoxia of the detrusor (13). After AUR is relieved, the reperfusion injury aggravates the damage to the detrusor (14). As a result, the function of the bladder could be affected by AUR. Our cystometric study showed that overdilatation could result in a decrease of maximum detrusor pressure and of bladder capacity and compliance. Detrusor overactivity or detrusor areflexia could also be the result of overdilatation. All these changes became more obvious with the increase of DOD.

We also found that the structural impairment of bladder

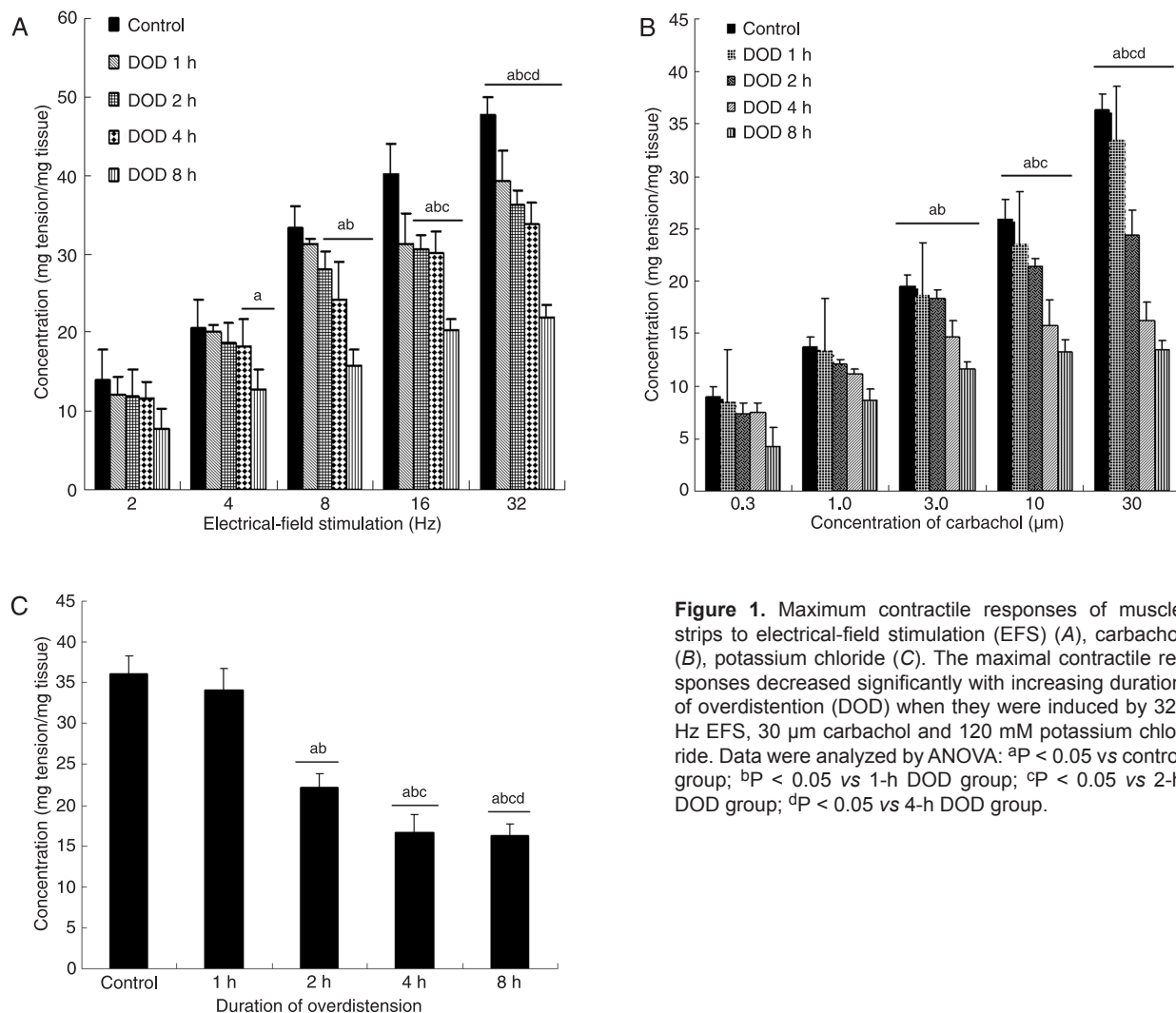


Figure 1. Maximum contractile responses of muscle strips to electrical-field stimulation (EFS) (A), carbachol (B), potassium chloride (C). The maximal contractile responses decreased significantly with increasing duration of overdilatation (DOD) when they were induced by 32-Hz EFS, 30 µM carbachol and 120 mM potassium chloride. Data were analyzed by ANOVA: ^aP < 0.05 vs control group; ^bP < 0.05 vs 1-h DOD group; ^cP < 0.05 vs 2-h DOD group; ^dP < 0.05 vs 4-h DOD group.

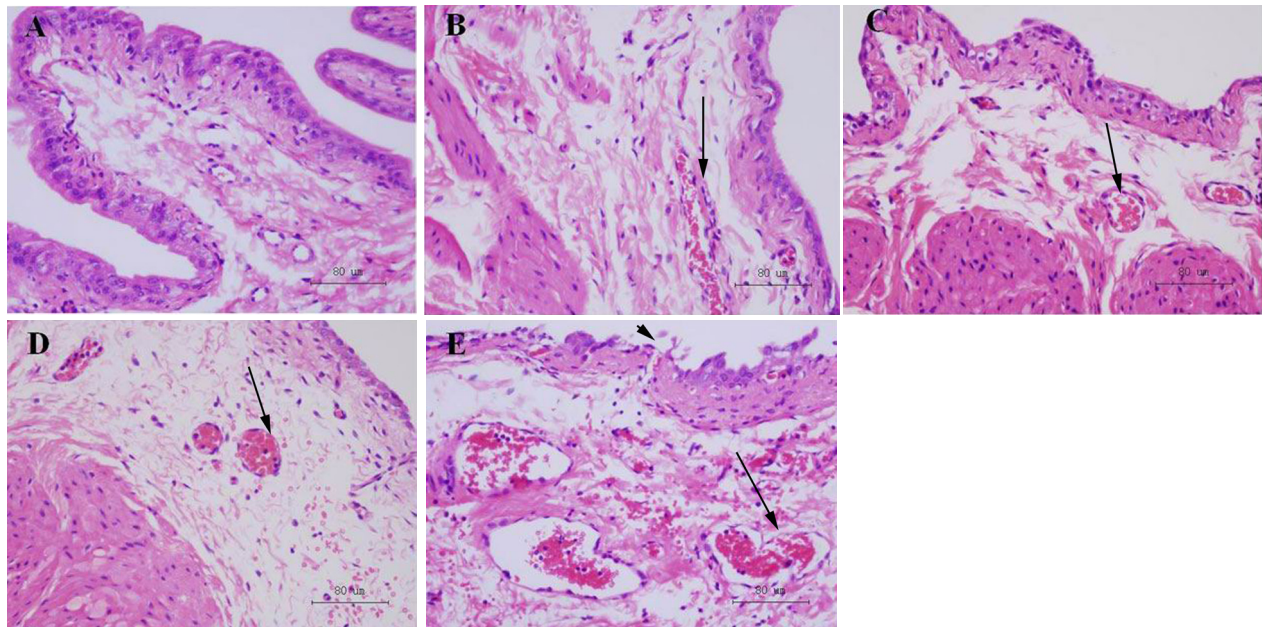


Figure 2. Morphological changes at different durations of overdistention (DOD) determined by microscopy with HE staining. Magnification bars = 80 μ m. *A*, Normal mucosa and submucosa; *B*, hemangiectasis in the submucosa, a few infiltrating inflammatory cells (arrow); *C*, hemangiectasis in the submucosa, more infiltrating inflammatory cells than in the 1-h DOD group (arrow); *D*, hemangiectasis and edema in the submucosa, more red blood cell leakage and infiltrating inflammatory cells (arrow); *E*, more obvious hemangiectasis and edema in the submucosa, obvious red blood cell leakage (arrow) and infiltrating inflammatory cells, some mucosal cells were sloughed (arrowhead).

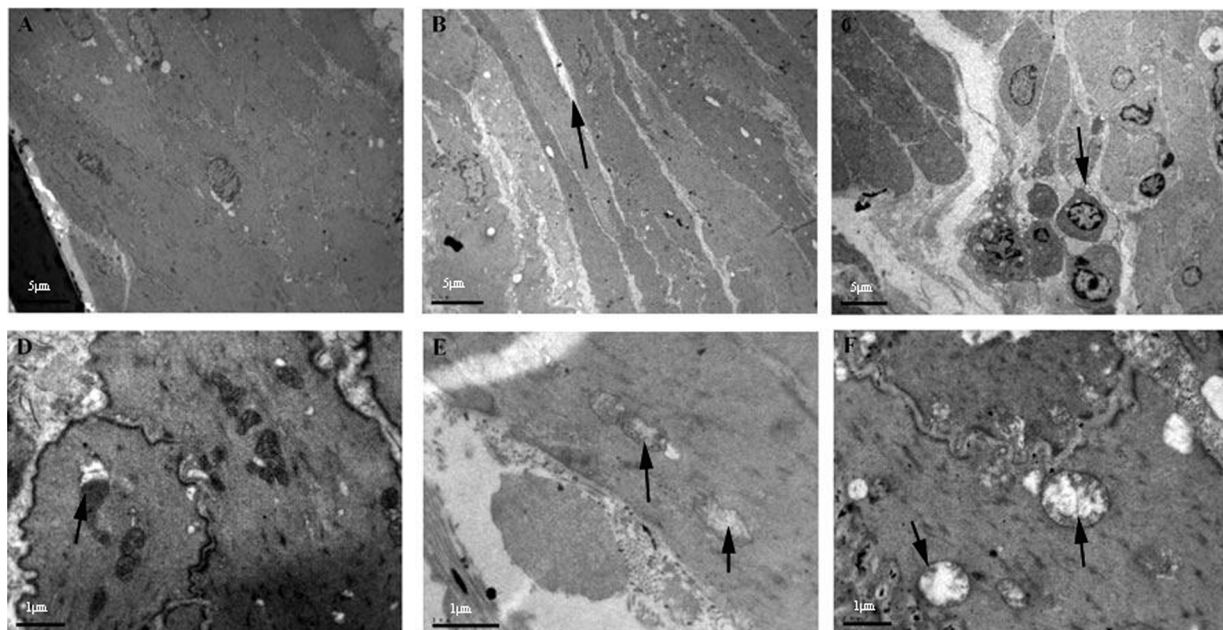


Figure 3. Ultrastructural changes at different durations of overdistention (DOD) observed by transmission electron microscopy. *A*, Control group, normal morphology of myocytes, arranged regularly with intact karyomorphism; *B*, 4-h DOD group, normal morphology of myocytes, arranged regularly with broadening intercellular space (arrow); *C*, 8-h DOD group, myocytes arranged in a disorderly manner, broadening intercellular space with infiltrating inflammatory cells (arrow); *D*, control group, normal mitochondria with tight intercellular connections (arrow); *E*, 4-h DOD group, ridges of mitochondria disappearing and vacuoles appearing (arrows); *F*, 8-h DOD group, swelling mitochondria without ridges, and more obvious vacuoles (arrows). Magnification bars: *A*, *B*, *C* = 5 μ m; *D*, *E*, *F* = 1 μ m.

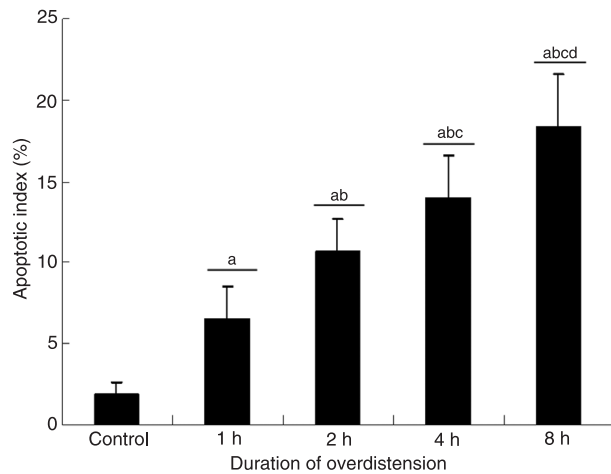


Figure 4. The apoptotic indexes of groups with different durations of overdistention (DOD). The apoptotic indexes increased significantly with increasing DOD. All data were analyzed by ANOVA: ^aP < 0.05 vs control group; ^bP < 0.05 vs 1-h DOD group; ^cP < 0.05 vs 2-h DOD group; ^dP < 0.05 vs 4-h DOD group.

tissue worsened with the duration of overdistention, while different layers of bladder tissue showed different severities of structural impairment: the mucosa and submucosa layers were prone to be injured, while the impairment of the muscle layer was usually slight. The possible reasons for these differences are as follows: first, the mucosa and submucosa metabolize actively and are more susceptible to ischemia and anoxia; second, owing to the rich vessels in the mucosa and submucosa, more WBCs exude after overdistention relief, releasing more active oxygen and hydrolytic enzymes that cause more serious tissue injuries; finally, muscle tissue has the strongest antioxidant ability. After observing slight changes in the detrusor by light microscopy, we further investigated it by transmission electron microscopy. As expected, the changes of morphology and organelles were not obvious at 1 and 2 h after overdistention relief. However, they became more obvious with the increase of DOD, such as a broader intercellular gap, inflammatory cell exudation, and swelling mitochondria with reduced ridges.

We used molecular biology techniques to detect how DOD affected the apoptosis-related factors in the rat bladder. We proved the important role of apoptosis and its related factors in the bladder dysfunction occurring after overdistention. With increased DOD, the expression of anti-apoptotic factors decreased, while that of pro-apoptotic factors increased, possibly resulting in the increase of apoptotic cells. The latter could contribute to the functional deterioration of the bladder. We also found that different layers of bladder tissue had different apoptotic rates, which were highest in the mucosa and submucosa and lowest in the detrusor. Anoxia and active substances released by exudated WBCs could induce cell apoptosis, while inflam-

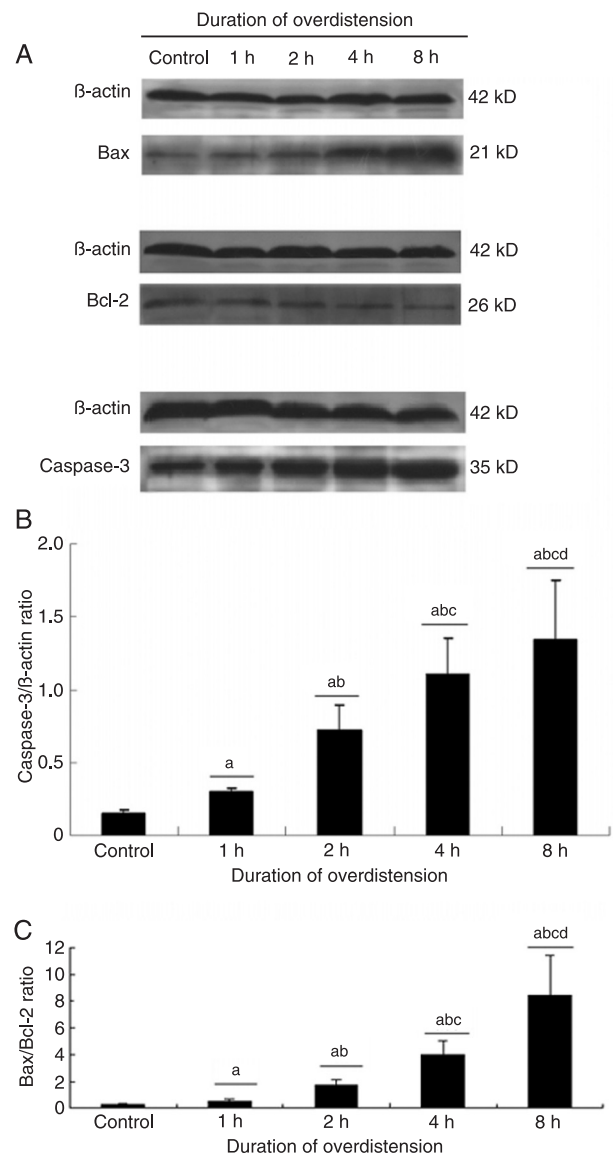


Figure 5. Effect of different durations of overdistention (DOD) on the expression of apoptosis-related proteins: *A*, Western blotting analysis of Bax, Bcl-2 and caspase-3, and β-actin as control. The pro-apoptotic factors Bax and caspase-3 were up-regulated, while the anti-apoptotic factor Bcl-2 was down-regulated with increasing DOD. *B*, Caspase 3/β-actin ratio in different DOD groups, which increased significantly with increasing DOD. *C*, Bax/Bcl-2 ratio in different DOD groups, which increased significantly with increasing DOD. All data were analyzed by ANOVA: ^aP < 0.05 vs control group; ^bP < 0.05 vs 1-h group; ^cP < 0.05 vs 2-h group; ^dP < 0.05 vs 4-h group.

matory exudates were most severe in the mucosal and submucosal layers, a fact that could explain the higher cell apoptosis rates in these layers. In addition, different layers of the bladder have different susceptibility to anoxia. The lowest apoptotic rates in the detrusor could be due to its

good tolerance to anoxia.

An interesting question that many urologists may ask is "when does bladder dysfunction pass the point of no return?". Our study may provide some clues to answer this question. At the beginning of AUR, inflammatory exudates and apoptosis are limited to the mucosa and submucosa, while the contraction function of the bladder is normal. With the increase of AUR duration, inflammatory exudates and apoptosis extend to the muscle but they are still slight, while the contractile function of the bladder begins to decrease. We think that bladder dysfunction in this phase could be completely reversed because of the mild injuries to the detrusor. With the advancement of AUR, the inflammatory exudates and apoptosis become more serious in muscle and may result in irreversible impairment of the detrusor and bladder dysfunction. However, how the AUR duration affects the recovery of bladder dysfunction should be further studied.

These results remind us that we should decompress the bladder as soon as possible and shorten the duration of AUR to protect bladder function when we treat patients with AUR, although we should treat the patients with AUR on an individual basis. Patients undergoing a longer time of AUR may need a longer time to recover bladder function. Catheterization should be prolonged in such patients in order to obtain a greater success rate of trial without catheter (15). A urodynamic test before transurethral resection of the prostate should be recommended to reduce the rate of surgical failure in patients with a longer time of AUR,

who might already suffer from an irreversible impairment of detrusor function (16).

Certainly, bladder overdistention is not equal to AUR, and clinical circumstances are more complicated than animal experiments. AUR usually is secondary to bladder outlet obstruction or detrusor dysfunction (17,18). The function and structure of the bladder may already have changed before AUR. In addition, other factors such as age and physical condition also contribute to the severity of impairment and the recovery of bladder function after AUR (19,20).

DOD plays an important role in functional and structural impairment of the bladder. Different DOD result in different severities of impairment of the rat bladder. With increasing duration, the inflammation and the injuries to ultrastructures of the bladder are more serious and the apoptotic rates and pro-apoptotic factors are up-regulated, while anti-apoptotic factors are down-regulated, all of which could contribute to more serious impairment of bladder function and structure.

Acknowledgments

We are very grateful to Mrs. Li Wang for meticulous technical assistance with transmission electron microscopy, and to Dr. Guo-hua Lin for his kind supervision of the contractile assay of muscle strips. Research supported by grants from the Department of Education of Zhejiang Province (#491010+G21078).

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